Reconstruction of Radiation-induced Injuries of the Lower Urinary Tract

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KEYWORDS

• Radiation • Urethra • Stricture • Bladder neck contracture • Brachytherapy • Urethroplasty

KEY POINTS

- Radiation therapy for prostate cancer has been used with increased frequency in the past 2 decades. Higher radiation doses with modern techniques seem to be a significant risk factor for formation of urethral stricture, bladder neck contracture, and rectourethral fistula.
- Radiation delivered to the apex of the prostate during interstitial therapy is a significant risk factor for the formation of urethral stricture in the bulbar and membranous urethra. Dose modifications may limit formation of urethral stricture.
- Intensity-modulated radiation therapy has shown no increased risk of lower urinary tract injury compared with three-dimensional conformal external beam radiation therapy.
- Urethral stricture caused by radiation therapy is often located in the bulbar and membranous region. Most of these strictures are short, and most often can be repaired with excision and primary anastomosis. Longer strictures are amenable to substitution urethroplasty.
- Rectourethral fistula caused by radiation therapy is a serious complication. Urinary and bowel function can be successfully restored with reconstruction in many patients.

INTRODUCTION

Radiation therapy for the treatment of prostate cancer has been evolving since its introduction in the early twentieth century. The discovery of radioactivity, the weak form of uranium, by Henri Becquerel in 1896 and the discovery of radium by Marie and Pierre Curie in 1898 ushered in a new era in medical technologies.[1] Early knowledge of the effects of radiation on human tissue was identified through incidental exposures by early researchers. The subsequent medical applications with this new technology attempted to maximize the dose of radiation and minimize the effects on normal tissue. The following 2 decades led to refined technologies and techniques of administration to prostate tissue through mainly intracavitary means that were used by prominent urologists of the era, including Hugh Hampton Young.[2] Benjamin Barringer is credited with pioneering the interstitial implantation techniques currently used via a perineal and suprapubic approach using glass-encapsulated radon.[3] The 1930s saw the first use of external beam radiation therapy (EBRT). More effective use of external and interstitial therapies now relies on modern imaging techniques of computed tomography (CT) scans and transrectal ultrasound to maximize treatment and limit side effects.[4]

Prostate cancer is the most common non–skin-related malignancy of men in the United States. In 2012, an estimated 241,740 new cases

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will be diagnosed, which accounts for 29% of all new cancer diagnoses in men.[5] According to the 2007 American Urological Association guidelines, use of either brachytherapy (BT) or EBRT may be used alone or in combination for first-line therapy for localized prostate cancer.[6] Analysis of the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) database, a national disease registry of more than 10,000 men, found that radiation therapy was used in more than 20% of newly diagnosed low-risk prostate cancer from 1993 to 2001.[7] This same study also showed an increase in the use of BT from 4% to 22% during the study time period. The SEER (Surveillance, Epidemiology, and End Results) database, which includes primarily men more than the 65 years of age, has shown a rapid adoption of use in recent years of intensity-modulated radiation therapy (IMRT), a modality of EBRT that can deliver high doses of radiation. The use of IMRT compared with three-dimensional conformal EBRT increased from 0.15% of total men treated with EBRT in 2000 to 95.6% in 2008.[8] Despite little knowledge of the long-term genitourinary morbidity, rapid adoption of high-dose IMRT and BT have become more prevalent in the treatment of prostate cancer.

Lower urinary tract injury caused by radiation treatment of pelvic malignancy includes formation of urethral stricture, bladder neck contracture (BNC), and rectourethral fistula (RUF). Each of these conditions can be a serious complication to the patient both physically and mentally. This article focuses on the pathophysiology, risk, evaluation, surgical reconstruction, and long-term considerations for patients with lower urinary tract injury caused by radiation therapy.

PATHOPHYSIOLOGY AND RISK FACTORS FOR LOWER URINARY TRACT INJURY

Radiation interacts with living cells in several ways that make it an effective cancer treatment. The effects may be divided into direct or indirect interactions with ionizing radiation. The direct interaction occurs when the energy from the photon directly damages either the cellular DNA and/or tissue protein. This damage leads to immediate cell death or mutation of the DNA. The indirect interaction occurs when the ionizing radiation interacts with water in the cell and leads to the formation of free radicals that interact with enzymes leading to cell death or future mutation. Both of these interactions lead to cellular injury that can cause division delay, reproductive failure, or interphase death through the apoptosis mechanism, which is more common in rapidly dividing cells.[9] These interactions and resultant cellular injury are dose dependent and occur in a linear threshold model. When normal tissue is damaged with exposure greater than the injury threshold, several changes occur that result in a cycle of scar and subsequent healing. Damage to basement membranes of vessels can lead to occlusion, thrombosis, and eventually reduced neovascularization.[10] The subsequent fibrosis is caused by an increase of fibroblasts that no longer make mature collagen, which accounts for the atrophy and contraction of the tissue.[11]

Urethral stricture results from replacement of the corpus spongiosum with fibrosis and resultant occlusion of the urethral lumen.[12] With a more thorough understanding of radiation biology it is logical that increases in radiation doses would result in a higher rate of urethral stricture. High-dose-rate BT (HDRBT) and EBRT, either alone or in combination, have been used to achieve higher disease-free survival for the treatment of prostate cancer.[4,13–16] This strategy has developed out of improved technology and imaging techniques that allow more focused concentration of radiation to the intended tissue. Data from the CaPSURE database showed the stricture rate for BT to be 1.8%, EBRT 1.7%, and combined therapy 5.2%.[17] Another more recent study compared the rate of stricture formation in 1903 patients after EBRT, low-dose-rate BT, and HDRBT. The rates of urethral stricture formation were 2%, 4%, and 11% respectively, indicating that despite modern imaging techniques and modifications the amount of radiation damage delivered to normal tissue is significant.[18]

The use of HDRBT has shown a high incidence of urethral stricture formation. Sullivan and colleagues[19] showed that after HDRBT the actuarial rate of urethral stricture formation at 6 years was estimated to be 12% for all urethral locations and 10.8% for the bulbomembranous location. Overall, the investigators concluded that 90% of urethral strictures following HDRBT occur in the bulbomembranous region. When combined with EBRT, HDRBT has a similar rate of stricture formation as HDRBT alone at 11.8%.[14]

As expected, the dose of radiation delivered to the urethra has been shown to be a significant risk factor in the development of urethral stricture as well as the location of the delivered radiation dosage. Merrick and colleagues[20] has shown that, in patients with urethral stricture formation following BT, the dose delivered to the apex of the prostate was significantly higher than in case-controlled patients who did not form urethral strictures. By limiting the dosage to the apex of the prostate, the investigators showed a relative risk reduction of stricture formation of greater than 30% Earley and colleagues[21] found that the radiation delivered by